REMARKS

Status of the Claims

Claims 34-44 and 58-61 are pending herein.

Support for new claims 58 to 61 can be found, for example, in paragraphs [0013], [0022] and [0100] to [0102] of the present application.

No new matter is added.

Information Disclosure Statement

Applicant appreciates the examiner's diligence in obtaining the foreign patent and literature references from the parent application.

Claim Rejection under 35 U.S.C. §112, second paragraph

Claims 34-44 are rejected under 35 U.S.C. §112, second paragraph. According to the Office, claims 34, 37, 39 and 40 are incomplete for omitting essential elements. This rejection is respectfully traversed.

Referring to paragraph 0025, the Office argues (a) that the disclosure stipulates that the amount of detergent must be low to avoid a washing step that would remove excess detergent, and (b) because the claim does not indicate the limit of detergent amount at which there would be a washing step, the scope of claims is not commensurate with what is disclosed to be essential to avoid filtration or washing.

The pertinent portion of paragraph 0025 reads as follows: "In other preferred embodiments, the detergent is a cationic detergent that is provided in the emulsion at a weight to weight detergent to polymer ratio of from about 0.001:1 to about 0.05:1. At these lower levels, there is typically no need for *a filtration or washing step* to remove excess detergent." (Emphasis added.)

Please note that the ratios disclosed are merely said to be typical for cationic detergents. Moreover, the fact that there is typically no need for a filtration or washing step to remove excess detergent at such lower ratios does not, by the rules of logic, compel a conclusion that it is necessary to filter or wash the microparticles at higher ratios.

Furthermore, even assuming for the sake of argument that this paragraph did teach that excess detergent must be removed at detergent to polymer ratios above about 0.05:1, the Office is still incorrect in asserting that the amount of detergent must be low to avoid a washing step that would remove excess detergent. The Office has apparently lost sight of the fact that, although claims 34, 37, 39 and 40 exclude a washing step, these claims do not exclude other methods for removing excess detergent, such as a filtration step. See, e.g., claim 36.

For at least these reasons, it is respectfully submitted that claims 34, 37, 39 and 40 do not omit essential elements.

Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph are requested.

Claim Rejections under 35 U.S.C. 102 and 103-Levy

Claims 34, 35 and 42-44 are rejected under 35 U.S.C. 102(e) as anticipated by US 6,395,253 to Levy et al. (Levy).

Claims 36, 37, 39 and 41 are said to remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levy. However, claims 37 and 39 were not previously rejected under 35 U.S.C. 103(a), but rather were objected to as being dependent upon a rejected base claim. Consequently, these claims were rewritten in independent form to include all of the limitations of the based claim and any intervening claims.

In any event, Applicant respectfully traverses these rejections and their supporting remarks.

In response to the prior Office Action mailed August 6, 2004, it was noted that, upon reviewing Levy, one of ordinary skill in the art would have followed Levy's procedures, as set forth in the Examples, to produce microspheres. In particular, Levy teaches a method of producing microspheres comprising forming a W/O/W emulsion, evaporating the organic solvent from the W/O/W emulsion, recovering microspheres by ultracentrifugation and washing recovered microspheres multiple times. This is in contrast to the present claims, in which a washing step is not included in the claimed

methods of producing a microparticle composition, i.e., the microparticles are not subjected to a washing step. Moreover, the present claims include the limitation that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles, with the remainder (i.e., 10-90%) unbound.

The Office agrees that Section 5.2.1 discloses a washing step, but argues that Sections 5.1 and 5.3 do not disclose washing steps. Section 5.1, however, is merely a description of materials, and otherwise has nothing to do with producing microparticle compositions.

Section 5.3 specifically states that the methodologies detailed in Section 5.2.1 (which explicitly discloses multiple washing steps) are followed, with the exception that poly-L-lysine was omitted from the second aqueous phase in the control microspheres (see, in particular, Section 5.3.1).

Concerning Section 5.3, the Office points to the disclosure of 0.1% SDS in Section 5.3.2 and notes that Levy teaches that SDS was required to disrupt the microspheres. However, it appears that the Office has failed to recognize that Levy's use of SDS occurred after formation of DNA containing microspheres and that SDS was used to disrupt the microspheres in order to release entrapped DNA from the microspheres (see col. 19, ll. 8-13). In particular, at column 19, lines 8-10, Levy specifically teaches incubating DNA-containing microspheres in excess TE buffer with and without 0.1% SDS. At column 19, lines 11-13, Levy discloses that SDS was used to establish that charge-related associations between poly-L-lysine and DNA contribute to the DNA release and/or extraction mechanism. Thus, in Section 5.3.2, the SDS was used as an analytical reagent to release condensed DNA from the microspheres. In contrast, in Applicants' claimed invention, detergent is used in a microparticle formation step. More specifically, detergent is included in step (a), in forming an emulsion.

Moreover, Levy does not even hint at the concept of the presently claimed invention, in which 10-90% of the total detergent in the microparticle composition remains unbound to the microparticles, thereby ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This

availability is accomplished in the presently claimed invention by not washing the particles.

In contrast, and as noted in paragraph [0011] of the present specification, washing the microparticles multiple times with water has been found to remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles (and thus less than 1% unbound). Because Levy teaches multiple washing steps, this reference cannot be said to teach or suggest a process for producing a microparticle composition like that claimed, in which 10-90% of the total detergent in the composition remains unbound to the microparticles.

In addition to ensuring that detergent is made available for complex formation with macromolecules, processes in which microparticles are not washed are also advantageous from a manufacturing perspective. In particular, processes in which microparticles undergo a washing step, such as the process described in Levy (Levy, in fact, utilizes multiple washing steps), also require a microparticle separation step (i.e., a centrifugation step). This is extremely unwieldy from a manufacturing standpoint. By avoiding the need for a separation step, however, the manufacturing process is greatly simplified, allowing for efficient scale up and for continuous manufacturing processing, as desired.

In summary, Levy's methods differ from Applicants' claimed methods in several aspects. For example, Levy 's methods provide for DNA entrapped microspheres, washing of the DNA-containing microspheres multiple times and incubating of the washed DNA-containing microspheres with buffer containing SDS to release the entrapped DNA from the microspheres. In contrast, Applicants' claimed methods provide for microparticles that are not subjected to a washing step, microparticle compositions in which about 10-90% of the total detergent is bound to the microparticles, with the remainder (i.e., 10-90%) unbound, and incubating of unwashed microparticle compositions with macromolecules to form a complex which is adsorbed on the surface of the microparticles.

For at least these reasons, it is respectfully submitted that Levy does not anticipate the claims or support a *prima facie* case of obviousness against the claims.

Reconsideration and withdrawal of the rejection of claims 34, 35 and 42-44 under 35 U.S.C. 102(e) as anticipated by Levy, and the rejection of claims 36, 37, 39 and 41 under 35 U.S.C. 103(a) as being unpatentable over Levy, are respectfully requested.

Claim Rejection under 35 U.S.C. 102-O'Hagan

Claims 34, 35, 42 and 43 are rejected under 35 U.S.C. 102(e) as anticipated by US 6,395,253 to O'Hagan et al. (O'Hagan). In particular, the Office contends that O'Hagan does not disclose a wash step. Applicant respectfully traverses this rejection and its supporting remarks.

O'Hagan clearly teaches washing steps. See, for instance, Example 1, col. 14, lines 62-63 (washed three times using centrifugation) and Example 3, col. 16, lines 3-4 (also washed three times using centrifugation).

Moreover, O'Hagan does not teach a process in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles, with the remainder (i.e., 10-90%) unbound.

For at least this reason, it is respectfully submitted that O'Hagan does not anticipate claims 34, 35, 42 and 43. Reconsideration and withdrawal of the rejection of claims 34, 35, 42 and 43 under 35 U.S.C. 102(e) as anticipated by O'Hagan, are respectfully requested.

Claim Rejection under 35 U.S.C. 103-Levy and Paliard

Claims 38 and 40 are rejected under 35 U.S.C. 102(e) as unpatentable over Levy in view of US 6,562,346, to Paliard et al. (Paliard). Applicant respectfully traverses this rejection and its supporting remarks.

Levy is discussed in detail above. In brief, Levy teaches DNA entrapped microspheres, washing of the DNA-containing microspheres multiple times and incubating of the washed DNA-containing microspheres with buffer containing SDS to release the entrapped DNA from the microspheres. As such, Levy would not have led one of ordinary skill in the art to carry out a method of producing a microparticle composition, like that claimed herein, in which the microparticles are <u>not</u> subjected to a

washing step, and in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles, with the remainder (i.e., 10-90%) is unbound.

Paliard, which cited for its disclosure of CTAB as a detergent, does not make up for the above noted deficiencies in Levy. For example, as elsewhere in the art at the time of the invention, washing is taught in Paliard in Example 5 (see col. 23, lines 53-55).

For at least the above reasons, it is respectfully submitted that the cited references do not support a *prima facie* case of obviousness against claims 38 and 40. Reconsideration and withdrawal of the rejection of claims 38 and 40 under 35 U.S.C. 103(a) as unpatentable over O'Hagan in view of Paliard are respectfully requested

CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

FEES

The Office is authorized to charge any additional fees required to deposit account number 50-1047.

CORRESPONDENCE

Please continue to direct all correspondence to Chiron Corporation.

Serial No. 10/775,964

Respectfully submitted,

David B. Bonham
Registration No. 34,297

Attorney for Applicant
Mayer Fortkort & Williams, PC
251 North Avenue West, 2nd Floor
Westfield, NJ 07090
Tel.: 703-433-0510
Fax: 703-433-2362

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David B. Bonham
(Printed Name of Person Mailing Correspondence)

(Signature)